REMARKS

Upon entry of the instant amendment, claims 1, 3, 5-7, 9-10 and 12-14 will remain pending in the above-identified application and stand ready for further action on the merits.

The instant amendment does *not* introduce any new matter into the application as originally filed. The amendment simply inserts the word "only" after the word "spraying" in claims 1, 3, 7, and 10, so that for example, claim 1 now recites "…spraying only a solution of a water soluble drug on a crystal of said water soluble drug substantially without using a binder or in the absence of binder in a rotary fluidized bed granulate coating apparatus…."

As such entry of the instant amendment at present is respectfully solicited.

Enclosed 37 CFR § 1.132 Declaration

Enclosed with the present response is a new 37 CFR § 1.132 Declaration of Mr. Yasushi Ochiai, one of the present co-inventors. In the accompanying Declaration of Mr. Ochiai, experiments are performed in order to show the importance of granular strength.

In section **"7. Results"** of Mr. Ochiai's 37 CFR § 1.132 declaration (see pages 6-8) the following results are shown:

7.1. Granular strength

Table 1 is a result of the measurement of the Riboflavin granules.

Table 1 Granular Strength of Riboflavin Granule

	(gf/mm^2)
Riboflavin granule 1 (PVP 10%)	619
Riboflavin granule 2 (PVP 15%)	727

7.2. Tablet hardness

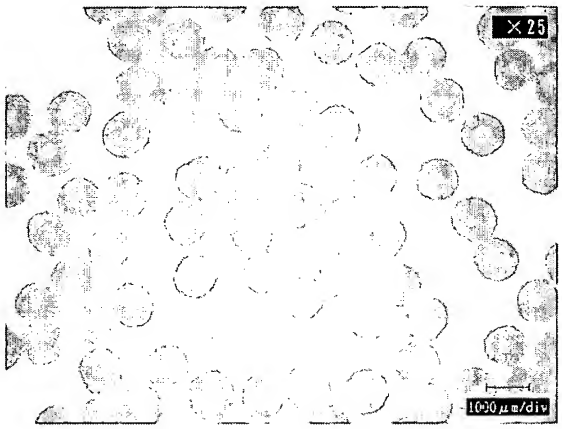
Table 2 shows hardness of the tablet obtained in Experiment 6.3. Both tablets have sufficient hardness as a pharmaceutical product.

Table 2 Tablet hardness

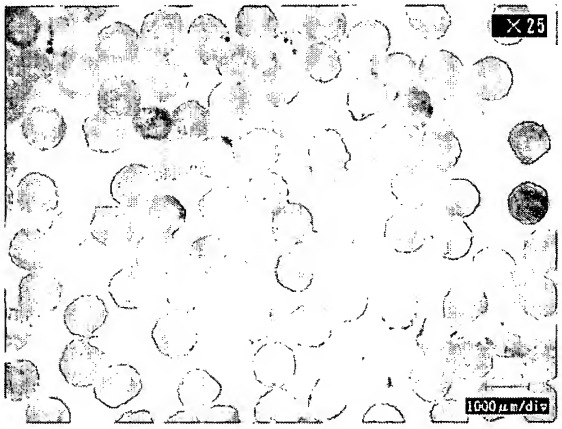
	(kg)
Tablet containing coated granule 1	2
Tablet containing coated granule 2	4.4

6.3. Acid-resistance disintegration test

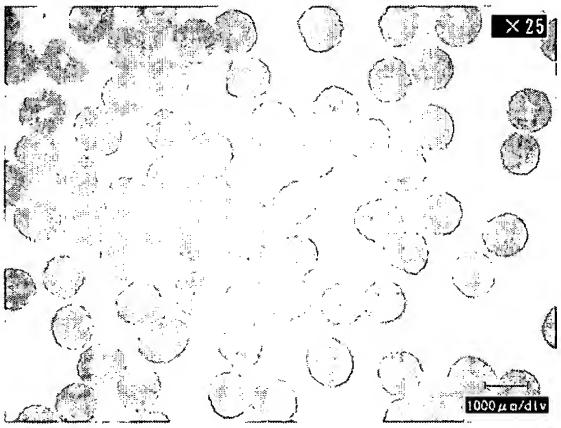
Coated granule 1



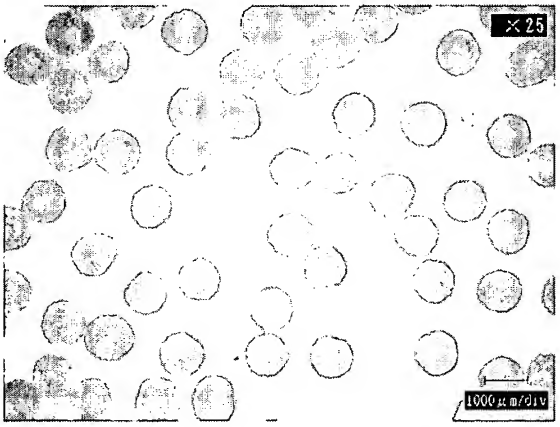
Coated granule 1 after tableting



Coated granule 2



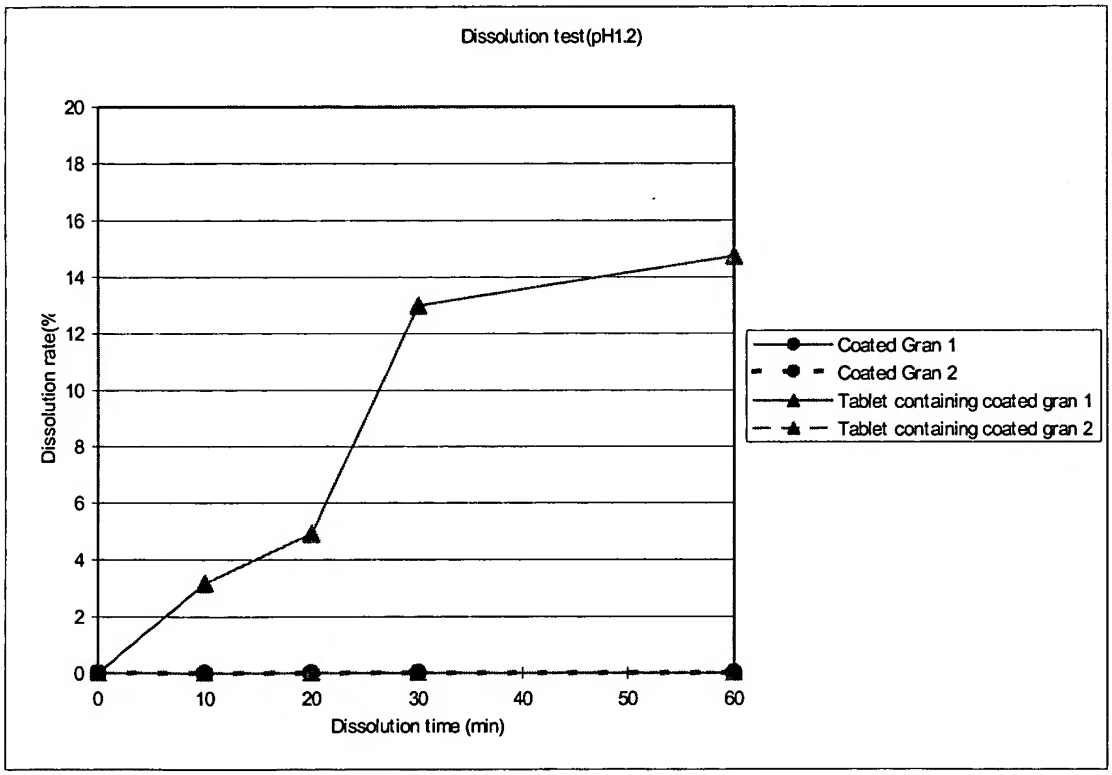
Coated granule 2 after tableting



There is not significant difference between the coated granule 1 and the coated granule 2. However, after tableting there is significant difference between the coated granule 1 and the coated granule 2. The coating film of coated granule 1 having less granular strength of 619g/mm^2 is damaged during tableting process. On the other hand the coating film of coated granule 2 having high granular strength of 727g/mm^2 is not damaged during tableting process and the coated granule shows good acid-resistance.

6.4. Dissolution test

In despite of the granular strength difference, the enteric coated granules do not release riboflavin to test solution of pH 1.2. The tablet of coated granules having less granular strength of 619g/mm^2 cannot maintain the acid-resistance and release riboflavin to test sample.



As described in the section **"8. Conclusion"** of Mr. Ochiai's enclosed declaration (see page 8):

We perform experimental only for the importance of granular strength. Nonpareil used in Koyama et al., does not have enough granular strength. We studied how to obtain granules having granular strength around

650g/mm^2. We found that certain amount of binder, such as polyvinylpyrrolidone (Povidone) is necessary to have granular strength of around 650g/mm^2.

The result of experimental result shows significant difference between the tablet of granule having granular strength of less than 650g/mm^2 and the tablet of granule having granular strength of more than 650g/mm^2. I believe that granular strength is important, especially during tableting process.

The granules of prior arts do not have enough strength for tableting without substantial amount of binder. On the other hand the granules of present invention does not need substantial amount of binder to have enough strength for tableting. Those are shown in this declaration and former declarations.

I believe that prior arts do not teach nor suggest the granule or method of manufacturing granule of present invention comprising a granulation step of spraying only a solution of a water soluble drug on a crystal of said water soluble drug substantially without using a binder or in the absence of binder in a rotary fluidized bed granulate coating apparatus, wherein the drug granule has a granular strength of 650-2500 gf/mm^2.

Accordingly, the enclosed declaration of Mr. Ochiai is pertinent to the Examiner's outstanding rejections under 35 USC § 103(a) set forth below, and thus the Examiner is requested to fully review the accompanying declaration at this time, inasmuch as all Comparative Testing set forth therein is supportive of the patentability of the present claims.

Claim Rejections Under 35 USC § 103

Claims 1, 3, 5-7, 9-10 and 12-14 are rejected under 35 USC § 103(a) as being unpatentable over Pierre et al. US '318 (US 5,300,318). Claims 1, 3, 5-7, 9-10 and 12-14 have also been rejected under 35 USC § 103(a) as being unpatentable over Koyama et al. US '914 (US 5,855,914). Reconsideration and withdrawal of each of these rejections is respectfully requested based upon the following remarks and the submission herewith of the accompanying Declaration of Mr. Yasushi Ochiai under 37 CFR § 1.132.

Legal Standard for Determining Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in

the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed

invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Present Invention and Its Advantages

The present invention relates to a method of manufacturing drug granules, and more particularly provides a pharmaceutical preparation containing a water-soluble drug as an active ingredient at a high density, which shows superior stability in a uniform content.

In the method of manufacturing a drug granule as instantly recited in claim 1, a granulation step occurs "of spraying *only* a solution of a water soluble drug on a crystal of said water soluble drug substantially *without using a binder or in the absence of binder in a rotary fluidized bed granulate coating apparatus*, wherein the drug granule has a granular strength of 650-2500 gf/mm^2." (See claim 1, *emphasis added*.)

An important aspect of the present invention relates to the granular strength of the granules, since it allows for the granules to be "tableted" or subjected to a "tableting" step, without breaking of the granules. This aspect of the present invention is also significant when the claimed inventive methods also contain a step of "coating said drug granule with a release control film coating agent." (*See* claims 7, 9-10 and 14.)

Distinctions Over the Cited Art

The above aspects of the present invention are nowhere taught, disclosed or otherwise rendered obvious by the disclosure of Pierre et al. US '318 or Koyama et al. US '914.

Pierre et al. US '318

For example, Pierre et al. (US '318) does not provide any suggestion regarding granular strength and/or tableting of coated

granules. In contrast to the teachings of Pierre et al. US '318, the present invention provides granules having sufficient granule strength to be capable of maintaining a coating film during tableting processes, and thereby also allow for the manufacture of tablets from the coated granules having desirable and suitable dissolution characteristics. On this point, the Examiner is invited to review Mr. Ochiai's accompanying Declaration, particularly the Figures and Tables provided therein, as well as Mr. Ochiai's two earlier filed 37 CFR § 1.132 declarations (filed with the USPTO on November 18, 2003 and June 24, 2004, respectively).

The method of claim 1 can also be distinguished from Pierre et al. US '318, since a "rotary fluidized bed granulate coating apparatus" is used by present inventors, which is different from the type of granulator taught by Pierre et al. US '318, and produces non-expected results when compared with Pierre et al. US '318. More particularly, unlike instant claim 1, which recites the use of a *rotary* fluidized bed granulator, Pierre uses an Uniglatt apparatus (which is a *non-rotary* fluidized bed coating device).

Further, there is provided no teaching or any information in the cited Pierre et al. US '318 reference that would lead one to the unexpected results that are associated with the present

invention. Which unexpected results are, namely, that a difference in *resistance ability to acid solution* is achieved with the present invention that is not envisioned, obtained or otherwise rendered obvious by the teachings and disclosure of Pierre et al. US '318.

Still further, even if one skilled in the art were to assume that generally speaking, the density of a granulate from a *rotary* fluidized bed granulator is much higher than that obtained from a fluidized bed coating device; nonetheless, in the cited Pierre et al. US '318 reference, there is provided no information about granular strength and/or properties of coated granules, and importantly, there are not obtained the advantageous results that are associated with the instant invention as claimed.

Koyama et al. US '914

As also evidenced in the accompanying Declaration of Mr. Ochiai, test results provided show that the granular strength of the present inventive granules is quite distinct and different from that of Koyama et al. US '914.

As noted by the Examiner in the outstanding office action at page 5, last paragraph "While Koyama et al do not teach the instant granular strength (650-2500 gf/mm^2), the Examiner points out that, generally differences in granular strength will not

support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such granular strength is critical." In response to this statement, Applicants direct the Examiner's attention to Mr. Ochiai's enclosed declaration and particularly sections 7 and 8 thereof, which were reproduced above for the Examiner's convenience. Upon giving proper consideration to the same, the Examiner will fully understand that the recitation of granular strength in the present claims is associated with an unexpectedly good property, which was not taught or envisioned in the teachings of the cited Koyama et al. US '914 reference, and which are not rendered obvious thereby.

Further to the above, Mr. Ochiai clearly states in the enclosed declaration that "The granules of prior arts do not have enough strength for tableting without substantial amount of binder. On the other hand the granules of present invention does not need substantial amount of binder to have enough strength for tableting." Mr. Ochiai further states "I believe that prior arts do not teach nor suggest the granule or method of manufacturing granule of present invention comprising a granulation step of spraying only a solution of a water soluble drug on a crystal of said water soluble drug substantially without using a binder or in the absence of binder in a rotary fluidized bed granulate

coating apparatus, wherein the drug granule has a granular strength of 650-2500 gf/mm^2."

Accordingly, based upon a consideration of the above remarks and the test results reported in Mr. Ochiai's accompanying 37 CFR § 1.132 Declaration and the remarks set forth above, it follows that the outstanding rejection under 35 USC § 103(a) of claims 1, 3, 5-7, 9-10 and 12-14 under 35 USC § 103(a) as being unpatentable over Pierre et al. US '318 or Koyama et al. US '914 must now be withdrawn.

CONCLUSION

Based upon the remarks presented herein, as well as the comparative testing results and conclusions based thereon set forth in Mr. Ochiai's accompanying 37 CFR § 1.132 Declaration, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 1, 3, 5-7, 9-10 and 12-14 are allowable at present.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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By _____
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4367-0101P

Attachment(s): 37 CFR § 1.132 Declaration of Mr. Yasushi Ochiai